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TOXICITY OF BARIUM CARBONATE TO RATS.

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PURPOSE OF INVESTIGATION.

A series of experiments on the toxicity of various substances to rats and their suitability for poisoning these animals was undertaken, in 1918, at the request of the Bureau of Biological Survey of the United States Department of Agriculture, for the purpose of obtaining toxicological data for use in connection with the rat-extermination work in the zone of occupation of the American Expeditionary Forces. Although this incentive ceased with the signing of the armistice, the studies have been continued because of their importance to agricultural economics as well as to the public health.

PREVIOUS INVESTIGATIONS.

The literature contains no references to work dealing with the toxicity of barium carbonate to rats, in spite of the fact that many articles give directions for its use as a rat poison and discuss its toxicity to other animals. The earliest communication which is of interest here is one by Crampe (5),[1] who recommended 20 per cent barium carbonate in bait for poisoning field mice. Lantz's (9) barium carbonate formula also calls for 20 per cent of this substance. Recently White (20) has reported good results from poisoning *Mus rattus* by the use of 25 per cent of barium carbonate. This concentration, however, was ultimately diluted, as water was added to the barium carbonate bait mixture. White set out individual baits containing 3 grains (200 mg.) of barium carbonate. If entirely con-

[1] The figures in parentheses refer to the bibliography at the end of this bulletin.

sumed, one such bait for a rat of average size would amount to 600 or 800 mg. of the poison per kilo. Storer (19) reported that calcium carbonate (whiting) protected rats and mice against barium carbonate as well as lead carbonate poisoning. There is, however, some uncertainty about these experiments, in the absence of definite quantitative poison and food-intake data.

An illustration of an old popular conception of the ideal rat poison which was held by some investigators is found in the following translation by Boelter (4) from Raebiger (15): "I have come to the conclusion that preparations which are really nonpoisonous are unable to kill rats, and poisons, call them what you like, if they kill rats will also kill domestic animals." Raebiger's results are in harmony with all known facts, and demonstrate the fallacy of the conception of a poison specific for rats.

As the toxicity of barium salts to other animals is of interest both to the user of barium rat baits and to the laboratory worker, a few citations (Tables 1 and 2) on this point are quoted.

TABLE 1.—*Toxicity to various animals of barium chlorid administered subcutaneously.*

Animal.	Salt.	Sublethal dose.	Lethal dose.	No. experiments.	Citation.
		Mg. per kilo.	*Mg. per kilo.*		
Rat	$BaCl_2$	35	45 to 89	Many	Table 4 (p. 4).
Do	do	40(?)	60	1	Bary (3).
Rabbit	do	20 and 46	50 to 75	5	Do.
Do	do	40 to 50	50 up	Many	Maurel (10).
Do	do		40 to 60	5	Kissner (8).
Dog	do		10 to 15		Aloy and Cournet (1).
Do	do		15 and 17	2	Schedel (17).
Do	do	6 and 10	15 to 20	5	Bary (3).
Do	do	4.5 to 14.3	9.1 and 14.3	2	Pilliet and Malbec (14).
Cat	do	15	18 to 60	5	Bary (3).
Chicken	do	40(?)	50 and 80	3	Do.
Pigeon	do	75	80 up		Maurel (10).
Do	do		60	1	Bary (3).

TABLE 2.—*Toxicity to various animals of barium salts administered per os.*

Animal.	Weight.	Barium salt.	Absolute dose.	Dose per kilo.	Result.	Citation.
	Kilo.		*Grams.*	*Grams.*		
Rat		$BaCl_2$		0.355 to 0.533	Fatal	Table 5 (p. 4).
Rabbit	1.177	$Ba(C_2H_3O)_2$	0.200	.170	do	Crawford (6).
Do	1.630		.500	.300	do	Do.
Do	1.800	$BaCl_2$		.170	do	Bary (3).
Sheep		do	4.000		Survived	Dieckerhoff (7).
Do		do	6.000		Fatal	Do.
Cattle		do	40.000		Survived	Do.
Horse		do	8.000 to 12.000.		Survived; therapeutic.	Do.
Do		do	[1] 15.000	.033	Fatal, with local effects in stomach from two boli.	Reynolds (16).
Dog	8.000 to 10.000.	do	.720 to .900	.090	Fatal	Aloy and Cournet (1).
Pigeon		do		.500	Survived [2]	Maurel (10).
Chicken		$BaCO_3$	1.333		Fatal	White (20).
Man		$BaCl_2$	[3] 8.6		Fatal in 10 hours	Stern (18).
Do		do	[3] 9		Fatal	Am. Med. Assoc. (2).

[1] Dose per 1,000 pounds of horse weight.

[2] Vomited.

[3] A. P. Chadbourne (personal communication) found that the lowest fatal dose of barium chlorid for man was that reported by Stern. Approximately 8.6 grams were fatal in 10 hours. In view of the proximity of the fatal and therapeutic doses reported (2), the fatal dose therein given would seem to be rather small.

Unfortunately, in some cases, exact lethal and sublethal doses are not known, since the amounts administered have not been based upon body weight. In other instances it has been necessary to calculate some of the figures from the authors' data. It would appear, however, that rabbits, chickens, and pigeons are about equally susceptible to barium administered subcutaneously, while cats and dogs are approximately three times as sensitive. Owing to differences in the physiology of the stomachs of the different species, and presumably to the differences in the average size between species, the toxicity of barium by mouth varies markedly, the purely species characteristic becoming more or less masked. For practical purposes, however, it may be assumed that the lethal dose of barium per os per kilo tends to decrease relatively as the size of the animal increases.

EXPERIMENTAL PROCEDURE.

In the experiments here reported the brown rat (*Rattus norvegicus*) was used as often as practicable. The domesticated white strain was employed for obtaining accurate food-intake data and for testing the relative efficiency of different percentages of barium carbonate in the bait. The melanotic strain was used in only a few toxicity experiments for purposes of comparison. The substitution of the white rat for the brown strain would seem fair, since the toxicity of barium to these two strains was found to be the same. The feeding experiments were confined, as far as possible, to the laboratory phase, although at times it was necessary to consider in some detail the practical aspects. In the experiments in which the stomach tube was used, the animals were first anesthetized with ether. The lethal doses are regarded, not as the minimum amounts which might be fatal, but those amounts which will kill a large proportion of the rats.

The barium chlorid administered was the ordinary crystalized salt ($BaCl_2 \cdot 2H_2O$). The carbonate, which was of high purity and free from soluble chlorid, was always used in the form of fine powder, having been passed through a 100-mesh sieve. The molecular weight and barium content of these preparations are given in Table 3, since their relative toxicity is determined on the basis of their barium content.

TABLE 3.—*Molecular weight and barium content of barium chlorid and barium carbonate.*

Salt.	Molecular weight.	Barium.	Conversion factor of barium into salt.
		Per cent.	
$BaCl_2 \cdot 2H_2O$..	244.32	56.2	1.778
$BaCO_3$.....	197.37	69.6	1.437
Ba.....	[1] 137.37	.....	.....

[1] Atomic weight.

RESULTS OF EXPERIMENTAL WORK.

The results from the subcutaneous and oral administration of barium chlorid are summarized in Tables 4 and 5, respectively.

TABLE 4.—*Toxicity of barium chlorid to brown rats (injected subcutaneously on the abdomen).*

Number of rats.	Barium chlorid in 0.65 per cent NaCl solution.	Barium.	Barium chlorid.	Fatalities.				
				16th hour.	24th hour.	Later.	Number.	Total per cent.
	Per cent.	*Mg. per kilo.*	*Mg. per kilo.*					
2	0.45	20	35	0	0	0	0	0
7	.45	25	45	0	0	3	3	43
3	.45	35	62	1	1	0	2	67
5	.45	50	89	1	0	3	4	80
1	.45	75	133	1	0	0	1	100
9	.45	100	178	8	0	0	8	89

TABLE 5.—*Toxicity of barium chlorid to brown rats (injected by stomach tube after preliminary light etherization).*

Number of rats.	Barium chlorid.	Barium.	Barium.	Fatalities.					
				16th hour.	24th hour.	Later.	Number.	Total per cent.	Average per cent.
	Per cent.	*Mg. per kilo.*	*Mg. per kilo.*						
6	3.5	100	178	1	0	0	1	17	17
2	1.7	200	355	0	0	0	0	0	57
5	3.5	200	355	4	0	0	4	80	
2	1.7	250	445		0	0	1	50	71
5	3.5	250	445		0	0	4	80	
2	1.7	300	533	2	0	0	2	100	100
5	3.5	300	533	5	0	0	5	100	

The subcutaneous lethal dose was from 45 to 89 mg. per kilo, and the oral lethal dose from 355 to 533 mg. per kilo. From this it would appear that barium chlorid is about six or seven times more toxic subcutaneously than per os.

The data obtained from the administration of barium carbonate in starch paste suspension by a stomach tube to etherized rats are given in Table 6.

TABLE 6.—*Toxicity of barium carbonate, 100 fine, suspended in starch paste (injected by tube after preliminary light etherization).*

Kind of rats.	Number of rats.	Barium carbonate in suspension.	Barium.	Barium carbonate.	Fatalities.					
					16th hour.	24th hour.	Later.	Number.	Total per cent.	Average per cent.
		P. ct.	*Mg. per kilo.*	*Mg. per kilo.*						
Brown	16	10	350	500	3	0	0	3	19	19
Do	7	10	400	630	5	0	1	6	86	85
White	6	10	400	630	2	0	3	5	84	
Brown	7	20	525	750	4	1	1	6	86	90
Black	7	20	525	750	2	2	2	6	86	
White	7	20	525	750	3	1	3	7	100	
Brown	7	10	700	1,000	5	2	0	7	100	92
Do	16	10	830 to 1,400	1,200 to 2,000	14	0	1	15	94	
Do	17	10	1,400	2,000	15	0	0	15	88	

From 630 to 750 mg. per kilo was found to be the least amount which could be considered efficient. On increasing the amount administered, however, there were still a few survivals, although the increased potency of the larger doses was clearly indicated by the relative increase of fatalities occurring within the first 16 hours. The occasional survival of an animal from a large dose would indicate that a 100 per cent mortality could not be expected.

Since it is possible for liquid to be forced through the pyloris under some conditions, these data have been checked against the results of feeding experiments (Table 7).

TABLE 7.—*Intake by hungry white rats of food containing 5 or 10 per cent barium carbonate.*

Weight of rat.	Amount of food eaten.	Barium carbonate in food.	Barium carbonate eaten.	Result.
Grams.	*Grams.*	*Per cent.*	*Mg. per kilo.*	
295	0.55	5	90	Lived.
159	.20	10	125	Do.
185	.25	10	135	Do.
184	.50	5	140	Do.
167	.25	10	150	Do.
286	.90	5	155	Do.
174	.30	10	170	Do.
198	.35	10	175	Do.
292	1.40	5	240	Dead within 48 hours.
310	1.55	5	250	Lived.
215	.55	10	255	Do.
192	1.00	5	260	Do.
245	1.40	5	285	Do.
330	2.45	5	375	Do.
206	1.55	5	375	Dead within 24 hours.
155	.65	10	420	Lived.
291	2.50	5	430	Do.
250	2.25	5	450	Dead within 40 hours.
175	.85	10	485	Dead within 48 hours.
343	3.50	5	510	Lived.
148	1.60	5	540	Do.
166	1.85	5	555	Do.
188	1.05	10	555	Do.
193	2.40	5	620	Dead within 16 hours.
160	1.00	10	625	Dead within 72 hours.
270	3.60	5	655	Dead within 40 hours.
264	3.50	5	655	Do.
215	1.45	10	665	Dead within 48 hours.
280	4.10	5	730	Dead within 40 hours.
320	4.70	5	735	Do.
170	2.60	5	765	Do.
252	3.90	5	775	Lived.
366	5.70	5	780	Dead within 40 hours.
175	1.40	10	800	Dead within 24 hours.
215	1.75	10	815	Dead within 48 hours.
205	1.70	10	830	Dead within 24 hours.
167	1.40	10	840	Do.
167	1.45	10	870	Do.
150	1.35	10	900	Do.
144	3.60	5	1,270	Dead within 20 hours.

The results of these two sets of experiments, given in the order of the barium carbonate intake per kilo, are in general agreement, the efficient lethal dose of barium carbonate being 630 mg. per kilo, or, more conservatively, 750 mg. On the basis of the barium content, this preparation of barium carbonate was from 57 to 75 per cent as potent as barium chlorid. In other words, approximately two-thirds of the carbonate was utilized in poisoning the animal. This does not mean, however, that every preparation of barium carbonate

possesses an equally favorable ratio of toxicity, since both fineness and physical texture undoubtedly influence the relative ease of disintegration and rate of solution.

MINIMUM EFFICIENT CONCENTRATION OF BARIUM CARBONATE.

Since the experiments already discussed have dealt with the toxicological consideration of barium, there remained to be determined the minimum concentration of barium carbonate in the poisoned bait which would give a high percentage of relatively quick fatalities. For these tests white rats were starved 12 to 24 hours before being fed the poison, to insure an empty stomach and a sharp appetite. The rat is a nocturnal animal and under ordinary circumstances probably would not be deprived of food for longer than 12 hours. A series of 14 rats, therefore, were starved for 12 hours and fed at 9 p. m. with the poisoned bait. As there was no marked difference between the results of this series and those of the experiments carried on in the daytime, with respect to both the average food intake and the percentage of fatalities from the concentration of barium carbonate used, it was concluded that the daytime experiments were valid.

It was occasionally observed for group tests that the average food intake varied somewhat, although the experiments were tried under as closely similar conditions as possible. For this reason the experiments were performed at widely separated intervals to minimize accidental influences and to make the general averages as representative as possible. Sometimes the same rats were used over again, in which instances no evidence was obtained of their having derived any benefit from their previous experience. Because of the fact that the rats used in these tests had been living upon the concentrated type of experimental diet and had accordingly adjusted their appetite or daily food intake, the averages expressed for this type of food might be slightly less than those which would have been secured by the use of a more bulky type of food. Such a possibility, however, is of minor importance, since it would favor the probability of fatal poisoning because of the larger amount of food which might be consumed.

Several series of starved rats were for an hour offered different types of diet, such as grain, dog biscuit, and soft, mealy food. The last-named food, which consisted approximately of 70 per cent peanut meal, 10 per cent milk powder, and 20 per cent lard, was usually consumed much faster, more of it was eaten before the appetite was satisfied, and less was scattered or wasted. In addition, the rapid consumption of food would occasionally seem very important, since a few rats fairly soon gave evidence of discomfort, due presumably to the relatively quick solution of the barium carbonate by the acid of the stomach, with consequent irritation.

The results obtained from feeding both poisoned and unpoisoned food are summarized in Tables 8 and 9. The rats were divided arbitrarily into weight groups, and the food intake calculated on the per rat and the per kilo basis. The probable errors are given for individual observations as well as for each group.

TABLE 8.—*Intake of control food (rats divided into weight groups).*

Weight group.	Number rats.	Weight.		Amount eaten.		Probable error.		Amount eaten per kilo.	Probable error.	
		Total.	Average.	Total.	Average.	Single.	Series.		Single.	Series.
Grams.		*Grams.*	*Grams.*	*Grams.*	*Grams.*			*Grams.*		
140 to 199	14	2,418	173	32.0	2.29	±0.79	±0.21	13.2	±4.6	±1.23
200 to 249	19	4,430	233	49.35	2.59	±0.48	±0.11	11.1	±2.1	±0.49
250 to 299	15	4,094	273	57.45	3.83	.....	.....	14.03	.....	.....
300 up	8	3,166	396	11.6	1.45	.....	.....	3.50	.....	.....
Total for 250 up	23	7,260	316	69.05	3.00	±0.78	±0.15	9.51	±2.5	±0.51
Total for all experiments	56	14,108	252	150.4	2.7	.....	.....	10.65	.....	.....

TABLE 9.—*Intake of food containing barium carbonate, all percentages (rats divided into weight groups).*

Weight group.	No. rats.	Weight.		Amount eaten.		Probable error.		Amount eaten per kilo.	Probable error.	
		Total.	Average.	Total.	Average.	Single.	Series.		Single.	Series.
Grams.		*Grams.*	*Grams.*	*Grams.*	*Grams.*			*Grams.*		
140 to 199	22	3,791	172	56.6	2.57	±0.65	±0.15	14.9	±3.88	±0.86
200 to 249	26	5,703	220	68.5	2.64	±1.3	±0.26	12.0	±5.92	±1.12
250 to 299	17	4,614	271	44.65	2.62	±1.0	±0.25	9.7	±3.72	±0.90
300 up	14	4,795	342	35.8	2.56	±0.79	±0.21	7.5	±2.30	±0.62
Total	79	18,903	239	205.55	2.60	.....	.....	10.85	.....	.....

Slightly greater variations occurred in the control series, and would seem to indicate the need of caution in too strict a mathematical interpretation. The data indicate, however, that on the average the food intake was approximately one one-hundredth of the rat's weight, both for the control and the barium-carbonate-fed series, from which it was concluded that the barium carbonate added to the diet was perfectly palatable. Just why the food intake per rat for all of the groups is approximately the same, when the stomachs of larger rats have greater capacity, is not at present clear. The greater food intake per kilo for the smaller rats is, under these circumstances, without significance.

For practical purposes, however, the individual food intake is the most important (Table 7), since the rats which eat scantily are the ones which necessarily determine the percentage to be placed in the diet, because they must also ingest a lethal dose. With this object

in view, different percentages of barium carbonate were fed. The results of these experiments are summarized in Table 10.

TABLE 10.—*Efficiency of different percentages of barium carbonate in the diet.*

Date.	Barium carbonate in food.	No. rats.	Type of experiment.	No. rats lived.	Fatalities.				
					16th hour.	24th hour.	48th hour.	Later.	Total.
1920.	*Per cent.*								*Per cent.*
Feb. 7	5	[1] 14	Individual, in very large cages.	6	0	2	6	0	.....
1919.									
Mar. 24	5	10	Individual, in very small cages.	5	0	1	1	3	.....
Feb. 15	5	10	.....do.....	6	([2])	1	2	1	.....
Mar. 8	5	10	.....do.....	6	([2])	1	3	0	.....
Total	5	44	.....	23	.....	5	12	4	48
1919.									
June 17	10	3	Individual, in very small cages.	2	([2])	1	0	0	.....
1920.									
Jan. 27	10	10	Group, in very large cages.	0	5	4	1	0	.....
May 5	10	10	.....do.....	5	([2])	1	1	3	.....
Total	10	23	.....	7	.....	11	2	3	70
1920.									
Jan. 27	20	15	Group, in very large cages.	0	13	2	0	0	.....
Feb. 1	20	11	Individual, in very large cages.	1	([2])	5	3	2	.....
Total	20	26	.....	1	.....	20	3	2	96

[1] Fed at night.

[2] No observation made.

About 50 per cent of the rats succumbed when fed 5 per cent barium carbonate. Most of the fatalities occurred after the twenty-fourth hour. On a diet containing 10 per cent, about 70 per cent of the rats died, the majority succumbing within the first 24 hours. Twenty per cent barium carbonate was even more efficient, only 5 per cent surviving and a great majority of fatalities occurring within the first 16 hours.

As already stated, the average food intake at a meal for the average hungry rat is one one-hundredth of the body weight, and from 630 to 750 mg. of barium carbonate per kilo may be regarded as the fairly certain fatal dose. When 5 per cent barium carbonate is fed in the bait it would be necessary for all rats to eat 12.5 to 15 grams per kilo, or one-eightieth to one sixth-seventh of their body weight. Some of the rats will do this and die, and a few of those which eat slightly less will succumb. This explains why about 50 per cent of the rats which were fed this diet died. When a 10 per cent barium carbonate bait is fed, a rat must eat one one-hundred-and-sixtieth to one one-hundred-and-thirty-third of its body weight, or 63 to 75 per cent of a meal of average size. A 70 per cent mortality on this concen-

tration is then readily comprehensible. In case of 20 per cent barium carbonate in the bait, it is necessary for the rats to consume only one three-hundred-and-twentieth to one two-hundred-and-sixty-sixth of their body weight, or 31 to 37 per cent of the average food intake, in order to ingest a lethal dose of barium carbonate. As a few will fail to do this and many eat much more, this concentration is efficient, as well as quickly fatal.

RESULTS OF EXPERIMENTAL WORK ON OTHER BARIUM COMPOUNDS.

Barium chromate was found to be nontoxic in doses as high as 2,000 mg. per kilo.

Barium soap, chiefly palmitate, was fairly toxic. Although not enough experiments were performed to definitely fix the lethal dose, it would seem to be approximately equal to that of barium carbonate. Its ease of hydrolysis apparently would favor the mobilization of the barium, upon which basis it would be more desirable than the carbonate. This fact, however, precludes its use in rat bait, since the hydrolysis occurring from a small amount of moisture would impart a disagreeable taste.

TOXICITY OF BARIUM CARBONATE TO ANIMALS OTHER THAN RATS.

Apparently rats are about as susceptible to barium administered subcutaneously as rabbits, chickens, and pigeons, and approximately one-third as sensitive as cats and dogs. When the barium is administered by mouth, however, the rat is comparatively the least susceptible of all the mammals cited, although the absolute amount is less, because of the small size of the rat.

If 20 per cent barium carbonate is used, it will be possible, on the basis of the recorded doses of barium chlorid, for adult animals to eat without fatal effects the following amounts of this rat bait: Sheep, one-half ounce; horses, 1½ ounces; and cattle, 5 ounces. Presumably, one and a half times this amount could be borne, since barium carbonate is less toxic than the soluble chlorid. The lethal dose of barium carbonate for chickens (20) is 20 grains, or one-fifth ounce, of rat bait containing 20 per cent of this poison. The danger to man, particularly children, is so very great that an amount of bait set for one or two rats might prove fatal.

CONCLUSIONS.

The lethal dose of barium compounds for rats is as follows: Barium chlorid, subcutaneously, 45 to 89 mg. per kilo; barium chlorid, by stomach tube, 350 to 535 mg. per kilo; barium carbonate, per os, 630 to 750 mg. per kilo. On the basis of the barium content, the carbonate is about two-thirds as active as the chlorid per os.

The average intake of food, both poisoned and unpoisoned, by hungry white rats used in these tests was one one-hundredth of their body weight.

Twenty per cent of barium carbonate in the rat bait was found to be an efficient concentration. With this percentage a rat is required to eat only one-third or three-eighths of a meal of average size, or one three-hundred-and-twentieth to one two-hundred-and-sixty-sixth of its own weight, in order to secure the ingestion of a lethal amount. With this concentration, many of the rats die within the first 24 hours, the chief factor being the consumption of an amount larger than the minimum efficient lethal dose.

From the results of both the pharmacological and the feeding tests, it would not seem advisable to always expect 100 per cent mortality from the administration of barium carbonate, in proper amounts, to rats.

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